REMARKS

Applicants respectfully request reconsideration of the present application in view of the presently submitted supplemental information, and in view of the reasons that follow. It is acknowledged that this communication is submitted after final rejection of the claims. However, because the supplemental information and remarks are believed to place the application in condition for allowance or at least in better condition for appeal, entry and consideration thereof by the Examiner is respectfully requested.

I. Status of the claims

Claims 1-5, 7-12 and 14-47 are pending and claims 1-5, 7, 8, 12, 14-22, 24-28, 30-43 and 47 are under examination.

II. Status of the rejections

Claims 1-4, 7, 8, 12, 14-22, 24-28, 30-43 and 47 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 1-5, 7, 8, 12, 14-22, 24-28, 30-43 and 47 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants continue to traverse the rejections for reasons of record.

III. The Advisory Action

In the Advisory Action dated June 17, 2009, the Examiner reasserted the prior written description rejection. The enablement rejection was not addressed, however.

IV. The Examiner Interview

Applicants thank Examiner Silverman for the courtesy of the Interview dated June 29, 2009, between the Examiner and Applicants' representatives, Christian Bauer and Simon Elliott. The Interview Summary omits that the Examiner considers Yang's teaching away to be limited to, or primarily concerning, microbial growth. Otherwise, the Interview Summary accurately reflects the substance of the Interview, including that claim 5 does not contain new matter and, as recited in the Interview Summary, the "Examiner and Applicants agreed that if evidence of aseptic techniques in pharmaceutical manufacturing, showing that the artisan

knows how to make and store dosage forms without microorganism growth is submitted, the enablement rejection will be overcome."

Applicants therefore provide herewith new evidence that directly addresses the Examiner's request.

V. The enablement rejection

A. Preliminary comments

Before addressing the issue of whether the person of ordinary skill in the art knows how to make and store the presently claimed dosage form, Applicants respectfully traverse the enablement rejection for reasons of record. More particularly, as to the issue of sterility of the claimed invention, Applicants reassert that the enablement of the present claims is not reliant upon demonstration that the claimed pharmaceutical products are sterile. In this regard, Applicants assert the following reasons.

First, Applicants are entitled to rely on Yang's teaching away regarding texture as a basis for nonobviousness without having to address the other teaching away by Yang, that of microbial contamination. Texture, alone, provides a legally sufficient reason to distinguish the claims from Yang. Moreover, texture is an element of the claim, unlike sterility. However, as explained during the Interview, the Examiner is of the opinion that the issue of texture is of none, or of secondary importance, to microbial growth. Applicants respectfully assert that this is incorrect as it is contrary to MPEP § 2164.05, which requires a determination of enablement to be based on the *evidence* as a whole, and without interjection of personal opinion ("The examiner should **never** make the determination based on personal opinion. The determination should always be based on the weight of all the evidence" MPEP § 2164.05, emphasis in original). Accordingly, it is appropriate to consider only Yang's explicit teaching, which regards the texture and microbial growth with *equal* importance.

Second, the claims do not recite sterility as an element of the claims. Applicants are only required to demonstrate enablement of the *claimed* invention and respectfully reassert that it is error to require enablement of non-existing elements in the claims.

> The enablement requirement under 35 U.S.C. § 112, first paragraph, requires that the specification describe the invention in such terms that one skilled in the art can make and use the claimed invention is to ensure that the invention is communicated to the interested public in a meaningful way. The information contained in specification must be sufficient to inform those skilled in the relevant art how to both make and use the claimed invention.

MPEP § 2164 (Emphasis Added).

Third, the assertion that the claims lack enablement is explicitly contradicted by Applicants' actual reduction to practice, as described in the specification.

Fourth, the requirement that the claimed products are safe and effective for clinical use imposes FDA requirements upon the claims, instead of, or in addition to, those required under 35 U.S.C. § 112. This is in error, under *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995).

Applicants respectfully believe that the claims are enabled, therefore. Nevertheless, as invited by the Examiner, Applicants submit the following evidence that microbial growth can be addressed by a person of ordinary skill in the art.

B. FDA guidance regarding oral dosage forms

Applicants submit as Exhibit A the FDA's "Guidance for Industry Specifications: Test Procedures And Acceptance Criteria For New Veterinary Drug Substances And New Medicinal Products: Chemical Substances" (June 14, 2006) (available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ Guidances/UCM052487.pdf, accessed July 20, 2009). Exhibit A demonstrates that the FDA adopts a flexible approach towards microbial contamination and safety for pharmaceutical products. For example, page 14 states that "[t]he type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the medicinal product." The microbial limits for solid oral dosage forms on pages 15-16, explicitly contemplate that the dosage form is not required to be sterile, but must only comply with acceptable levels of bacterial contamination, stating that "acceptance criteria should be set for the total count of aerobic microorganisms, the total count of yeasts and molds, and the

absence of specific objectionable bacteria" *Id.* at page 15. *See also* decision tree 6, page 29; and decision tree 8, page 33, showing relevant factors that may be considered. Where an antimicrobial preservative is indicated, similar acceptance criteria should be developed, noting:

> For oral liquids needing an antimicrobial preservative, acceptance criteria for preservative content should be established. Acceptance criteria for preservative content should be based upon the levels of antimicrobial preservative necessary to maintain microbiological quality of the product at all stages throughout its proposed usage and shelf-life. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test.

Id. at page 16.

Sterility may be required for some products, such as parenteral formulations (*i.e.*, injectable). Such products may be terminally sterilized, for example. *Id.* at page 8. Where sterility is required, Exhibit A also mandates the development of appropriate procedures for testing and acceptance criteria. *Id.* at page 18.

Where sterility is required, but terminal sterilization is not feasible, aseptic processing may be used. The attached FDA guide on aseptic processing, "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice (September 2004) (available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf, accessed July 20, 2009) is submitted herewith as Exhibit B. Exhibit B distinguishes between terminal sterilization, in which all components in their final packaging are sterilized, and aseptic processing, in which previously sterilized components are brought together under aseptic conditions. *See id.* pages 2-3. More generally, Exhibit B provides guidance on the practice of aseptic techniques for pharmaceutical compositions, monitoring and testing procedures to ensure appropriate quality control, *etc.* Exhibit B is evidence that aseptic processing is

known and used by those of ordinary skill in the art, and is FDA-approved as a means of obtaining sterile compositions without terminal sterilization.

Microbial contamination is of less concern when the product is made shortly before use, such as when made by a compounding pharmacy. As noted at page 2 of "Compliance Policy Guides Manual, Sec. 460.200, Pharmacy Compounding" (May 2002) (available at www.fda.gov/downloads/Drugs/ GuidanceComplianceRegulatory Information/Guidances/ ucm124736.pdf, accessed July 20, 2009), submitted herewith as Exhibit C, "The FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner." Compounding pharmacies are regulated under state law, *id.* at pages 2-3, and so requirements vary.

C. The claims are enabled

In conclusion, Applicants assert that enablement of the present claims is not reliant on whether the claimed compositions are sterile. Applicants are not required to demonstrate sterility, or any impact on microbial growth, for Applicants to rely on Yang's teaching away. Applicants are not required to demonstrate sterility, as is not an element of the claims and, even if it were implied by the recitation of a pharmaceutical composition, it is incorrect to require FDA standards to the question of enablement.

Nevertheless, were one to apply FDA standards, the person of ordinary skill in the art would be able to meet them. First, the FDA does not require that oral dosage forms be sterile, only that reasonable limits be set, according to the product and its intended use. The issue of microbial growth can be addressed in several ways. First, the compositions of the invention may be made by a compounding pharmacy shortly before use. As the composition is not stored for any extended period, microbial growth is less of a concern. Second, if the person of ordinary skill sought to control growth, a preservative may be added. If sterility is required, however, the person of ordinary skill could prepare the composition and terminally sterilize it or, if infeasible, prepare the composition under aseptic techniques.

Therefore, the "problem" of microbial growth, to the extent that it may be relevant to the present claims, is not insurmountable. Instead, this problem may be addressed by the person of ordinary skill through several different means, without undue experimentation, and in accordance with FDA guidelines. Applicants respectfully believe that the present rejection is overcome and request its reconsideration and withdrawal, therefore.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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